Regional haemodynamic effects of human α - and β -calcitonin gene-related peptide in conscious Wistar rats

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1 A comparative study was carried out to assess the regional haemodynamic effects of intravenous infusion of human α - and β -calcitonin gene-related peptide (CGRP; 0.006, 0.06 and 0.6 nmol h⁻¹) in conscious, unrestrained Wistar rats.

2 With human α -CGRP, tachycardia was always accompanied by a fall in mean arterial blood pressure (MBP), but human β -CGRP at the middle dose caused tachycardia with no significant hypotension.

3 Human α - and β -CGRP both caused dose-dependent falls in MBP accompanied by common carotid and hindquarters vasodilatations and increased flows. The highest dose of α - and β -CGRP caused mesenteric vasoconstriction and renal vasodilatation, but the latter was not associated with an increase in flow.

4 With the intermediate dose, human α -CGRP caused more significant haemodynamic changes than did human β -CGRP. In addition, comparison with previous experiments involving infusion of rat α -CGRP indicated that human α -CGRP had more potent haemodynamic effects than the former.

Introduction

In a previous study we found that intravenous infusion of rat α -calcitonin gene-related peptide (CGRP) in conscious Wistar rats caused differential, dose-dependent, regional haemodynamic effects (Gardiner *et al.*, 1989). There were vasodilatations in renal, hindquarters and common carotid vascular beds, although only in the latter two regional circulations were flows increased above baseline, and the effect in the common carotid vascular bed was about double that in the hindquarters. In spite of direct evidence for a vasodilator effect of CGRP on the superior mesenteric vascular bed *in vitro* (Marshall *et al.*, 1986a), hypotensive doses of rat α -CGRP caused clear-cut superior mesenteric vasoconstriction, with the increase in vascular resistance being associated with a significant reduction in flow below baseline. The magnitude of the heart rate (HR) responses to rat α -CGRP indicated a possible direct cardiac effect of the peptide in addition to baroreflex-mediated influences.

These results are consistent with rat α -CGRP having potent cerebral vasodilator properties (McCulloch *et al.*, 1986; Uddman *et al.*, 1986; Edvinsson *et al.*, 1987) and positive chronotropic effects (Marshall *et al.*, 1986b; Sigrist *et al.*, 1986). One possible explanation of the lack of mesenteric vasodilatation with infusion of CGRP is that reflex effects override the dilator actions of CGRP. If this were the case, then low doses of CGRP, that were without effects on mean arterial blood pressure (MBP), might reveal a primary mesenteric vasodilator action. In the present study we addressed this possibility and also assessed the cardiac effects of the same manoeuvre.

Since there are several molecular forms of CGRP (see Zaidi *et al.*, 1987) it is theoretically possible that the haemodynamic profiles of the various peptides might differ such that there was a relative enhancement of a particular feature of the cardiovascular actions of one of the species. We investigated this possibility by carrying out a systematic comparison of the regional haemodynamic effects of human α -

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and β -CGRP in conscious rats. The dose-range chosen was based on our previous findings, but included infusion of CGRP at $0.006 \text{ nmol h}^{-1}$, i.e., 10 fold lower than previously used.

Our overall objectives can be stated formally as the following questions: (1) Does infusion of human α - or β -CGRP at a low dose produce positive chronotropic effects independent of changes in MBP? (2) Does infusion of human α - or β -CGRP at a low dose produce superior mesenteric vasodilatation? (3) Do infusions of a range of doses of human α - or β -CGRP have similar regional haemodynamic effects?

By reference to our previous investigations (Gardiner *et al.*, 1989) we were also in a position to consider the possibility that rat and human α -CGRP have different haemodynamic profiles.

Methods

Male, Wistar rats (from Bantin and Kingman) were used in this study. At the time of operation animals weighed between 330–420 g. Details of the methods used have been described elsewhere (Gardiner *et al.*, 1989). Under anaesthesia (sodium methohexitone 60 mg kg^{-1} i.p., supplemented) pulsed Doppler probes (Haywood *et al.*, 1981) were implanted around left renal and superior mesenteric arteries and the distal abdominal aorta (below the level of the ileocaecal artery) or, in other animals, around both common carotid arteries. At least 1 week after operation all animals that were growing normally, grooming, etc., and with acceptable signals from all 3 probes (signal : noise ratio $> 20 : 1$) were briefly re-anaesthetized (sodium methohexitone 40 mg kg^{-1}) and had intravascular catheters implanted (in the abdominal aorta via the caudal artery and in the right jugular vein) and the probe wires soldered into a microconnector clamped in a harness fitted to the rat.

No measurements were made until the following day when, at 06 h 15 min, continuous recordings of MBP, instantaneous HR, and renal, mesenteric and hindquarters, or bilateral common carotid Doppler shift signals were begun. Measurements were made whilst the animals were unrestrained in their home cages. Phasic Doppler shift signals were monitored to ensure their acceptability and mean Doppler shift signals were obtained from them electronically. Changes in Doppler shift signal give a reliable index of changes in volume flow (Haywood *et al.*, 1981; Wright *et al.*, 1987) and these were calculated as % of the baseline level. From the MBP and mean Doppler shift, % changes in vascular resistances were calculated relative to the baseline level (Haywood *et al.*, 1981).

The experimental protocol ran over 2 days and animals were randomized to receive human α - or β -CGRP on the first experimental day. All animals received human α -CGRP on one day and human β -CGRP on the other day, both peptides being given as 60 min infusions at 3 different doses (0.006 , 0.06 and 0.6 nmol h^{-1} ; 0.3 ml h^{-1}). The infusate consisted of CGRP dissolved in isotonic saline containing 1% bovine serum albumin and 0.05% lactose. The amount of peptide needed to achieve the desired concentration was calculated from the stated peptide content of the lyophilizate. CGRP was given in increasing doses since the effects of higher dose infusions are persistent (Gardiner *et al.*, 1989). Each infusion was separated by at least 1 h such that variables had returned to baseline levels for a minimum of 30 min before any subsequent infusion of CGRP was begun. The infusion rate was 0.3 ml h^{-1} for all doses of both peptides. Infusion of vehicle at the same rate had no consistent effects. One-hour infusions of human α -CGRP at repeated intervals of 1 h cause reproducible cardiovascular effects in our model (Gardiner, S.M., Compton, A.M. & Bennett, T., unpublished observations).

Measurements were made at 0, 5, 10, 20, 30, 40, 50, 60, 65, 70, 80, 90, 100, 110 and 120 min, with the infusion running between 0 and 60 min. Data were analysed by two-way, non-parametric analysis of variance (Friedman's test). In the text where effects were referred to, then $P < 0.05$ indicates a significant result.

Peptides: human α -CGRP was obtained from Celltech Ltd., (Lot No. 05543GT00-02) and human β -CGRP was obtained through Celltech Ltd., (manufactured by Peninsula Labs).

Results

Human α - or β -CGRP infusion at $0.006 \text{ nmol h}^{-1}$

Animals with renal, mesenteric and hindquarters probes α -CGRP had no significant effect on MBP or HR. During the infusion, there was a slight, transient reduction (at 30 min) in mesenteric flow, but no significant changes in renal or hindquarters flows. Following infusion there were small reductions in renal (65–120 min) and mesenteric (70–120 min) flows, associated with vasoconstrictions (renal, 70–120 min; mesenteric, 60–120 min); there were no changes in hindquarters haemodynamics. Measurements made in animals not receiving CGRP but made during the same times of day as those receiving the low dose of α -CGRP, showed a similar drift in renal flow and resistance, indicating these changes were probably a consequence of the light-dark transition (the latter ending at 5 h 00 min). A similar drift

Figure 1 Cardiovascular variables during and after infusion (indicated by stippled horizontal bar) of human α -calcitonin gene-related peptide (α -CGRP) (○) or human β -CGRP (●) at 0.06 nmol h^{-1} (a) or 0.6 nmol h^{-1} (b). The values show the group mean ($n = 8$) with representative s.e.means. The time points at which values were significantly different from baseline are indicated by asterisks.

was seen in renal haemodynamics in animals receiving β -CGRP, but no other significant changes occurred during or after infusion of this peptide.

Animals with bilateral common carotid probes There were no significant changes in any measured variable during or after infusion of α -CGRP.

During infusion of β -CGRP, there were no changes in MBP or HR, but there were small reductions in left (20 min) and right (60 min) common carotid flows, associated with vasoconstrictions (left 20, 60 min; right 50, 60 min). Since, after infusion of β -CGRP, there were significant reductions in common carotid flows (left, 65, 70, 80, 90, 110, 120 min; right 65, 70, 80, 110, 120 min) and increases in vascular resistances (left 65, 70, 80, 110, 120 min; right, 65, 70, 80 min) that were not seen in the same

animals given α -CGRP at the same time of day, it is possible these effects were related to the administration of β -CGRP.

Human α - or β -CGRP infusion at 0.06 nmol h^{-1}

Animals with renal, mesenteric and hindquarters probes Infusion of α -CGRP was associated with a fall in MBP and a tachycardia (Figure 1). Renal blood flow was unchanged, but there was a reduction in mesenteric and an increase in hindquarters flow (Figure 1). Calculated renal vascular resistance fell and there was a hindquarters vasodilatation but no significant change in mesenteric vascular resistance (Figure 2).

Infusion of β -CGRP had variable effects on MBP such that, overall, there was no significant change,

Figure 2 Calculated vascular resistances during and after infusion (indicated by stippled horizontal bar) of human α -calcitonin gene-related peptide (α -CGRP) (○) or human β -CGRP (●) at 0.06 nmol h^{-1} (a) or 0.6 nmol h^{-1} (b). The values show the group mean ($n = 8$) with representative s.e.means. The time points at which values were significantly different from baseline are indicated by asterisks.

although there was a tachycardia (Figure 1). β -CGRP had no effect on renal flow (Figure 1) or resistance (Figure 2), and the reduction in mesenteric blood flow it produced (Figure 1) was not accompanied by a significant change in resistance (Figure 2). However, during infusion of β -CGRP there was an increase in hindquarters flow (Figure 1) that was accompanied by vasodilatation (Figure 2). Following infusion of β -CGRP there was a reduction in hindquarters flow (Figure 1) associated with vasoconstriction (Figure 2).

Thus, the effects of α - and β -CGRP were similar in the mesenteric vascular bed where the fall in flow was associated only with a tendency towards vasoconstriction. However, it is notable that the lack of significant effect of β -CGRP on MBP was accompanied by a less sustained hindquarters vasodilatation than was seen with α -CGRP. Furthermore, there was a post-infusion hindquarters vasoconstriction with β -CGRP that was not seen with α -CGRP (Figure 2).

Animals with bilateral common carotid probes Administration of α -CGRP was accompanied by a reduction in MBP and an increase in HR (Figure 3), similar to those seen in animals with renal, mesenteric and hindquarters probes (Figure 1). These changes were accompanied by increases in common carotid flows (Figure 3) associated with decreases in vascular resistances (Figure 4).

Although the tachycardias induced by human β -CGRP were similar in magnitude to those induced by human α -CGRP, the former did not have a sustained hypotensive effect (Figure 3). The increases in common carotid flow were not as persistent as those seen with human α -CGRP (Figure 3), and this was reflected in the truncated common carotid vasodilatations seen with β -CGRP (Figure 4).

Human α - or β -CGRP infusion at 0.6 nmol h^{-1}

Animals with renal, mesenteric and hindquarters probes Infusion of α -CGRP was accompanied by hypotension and tachycardia (Figure 1). Renal and mesenteric flows were reduced and hindquarters flow was increased (Figure 1). There were renal and hindquarters vasodilatations (Figure 2), and a mesenteric vasoconstriction. After infusion, there was a significant bradycardia and a secondary fall in MBP accompanied by a renal vasodilatation, but no other changes (Figures 1 and 2).

Infusion of β -CGRP caused a tachycardia similar in magnitude to that seen with α -CGRP (Figure 1), but the fall in MBP was less marked and persistent (Figure 1). Renal flow was not significantly affected by β -CGRP, and the reduction in mesenteric flow was not as prolonged as with α -CGRP (Figure 1).

Figure 3 Cardiovascular variables during and after infusion (indicated by stippled horizontal bar) of human α -calcitonin gene-related peptide (α -CGRP) (O) or human β -CGRP (●) at 0.06 nmol h^{-1} (a) or 0.6 nmol h^{-1} (b). The values show the group mean ($n = 8$) with representative s.e.means. The time points at which values were significantly different from baseline are indicated by asterisks.

However, the increase in hindquarters flow with β -CGRP was similar to that seen with α -CGRP (Figure 1). Infusion of β -CGRP was associated with renal and hindquarters vasodilatations not different from those seen with α -CGRP (Figure 2). However, the mesenteric vasoconstriction was more rapid in offset and followed by a brief vasodilatation (Figure 2). Furthermore, there was no bradycardia following β -CGRP infusion (Figure 1), and no secondary fall in MBP (Figures 1 and 2).

Animals with bilateral common carotid probes Infusion of α -CGRP produced a reduction in MBP associated with a tachycardia (Figure 3). There were marked increases in common carotid flow associated with vasodilatations (Figures 3 and 4). After infusion, carotid haemodynamics returned to baseline levels,

but there was a post-infusion bradycardia and secondary fall in MBP (Figures 3 and 4), similar to the picture seen in the animals with intra-abdominal probes (Figure 1).

Infusion of β -CGRP produced falls in MBP, increases in HR, increases in common carotid flow and decreases in resistance, similar to those seen with α -CGRP (Figures 3 and 4). However, as with the animals bearing intra-abdominal probes, there was no bradycardia or secondary fall in MBP following infusion of β -CGRP.

Discussion

It is clear that the present study did not demonstrate a positive chronotropic effect of human α -CGRP

Figure 4 Calculated regional vascular resistances during and after infusion (indicated by stippled horizontal bar) of human α -calcitonin gene-related peptide (α -CGRP) (○) or human β -CGRP (●) at 0.06 nmol h^{-1} (a) or 0.6 nmol h^{-1} (b). The values show the group mean ($n = 8$) with representative s.e.means. The time points at which values were significantly different from baseline are indicated by asterisks.

independently of any change in MBP, although human β -CGRP at a dose of 0.06 nmol h^{-1} was without significant effects on MBP at a time when it caused an increase in HR. Moreover, in some animals, administration of human β -CGRP at 0.6 nmol h^{-1} caused an increase in HR unaccompanied, initially, by any detectable change in MBP. However, without detailed information about central

haemodynamics and the transmural pressures experienced by the baroreceptors, it is not possible to exclude a change in afferent signalling as contributing to the changes in HR. In fact, it is feasible that the cardiac effects of human β -CGRP acted to offset any fall in MBP due to vasodilatation. While it could be argued that *in vitro* results support the belief that changes in HR with CGRP *in vivo* may be due to direct actions (Sigrist *et al.*, 1986; Marshall *et al.*, 1986b; Asimakis *et al.*, 1987), the doses of CGRP used in the *in vitro* studies are usually much higher than those that cause tachycardia *in vivo*. In addition, although a recent investigation by Howden *et al.*, (1988) showed that bolus doses of human α -CGRP in conscious human volunteers caused increases in HR with no statistically significant effect on systolic or diastolic BP, the data indicate that some subjects probably did show a fall, particularly in diastolic BP. Struthers *et al.*, (1986) found that infusion of human α -CGRP did cause falls in diastolic BP and increases in HR in volunteers. Furthermore, their analysis of the change in BP and HR with CGRP, compared to other vasodilators, did not indicate an unexpected tachycardia with this peptide. While the original descriptions of the cardiovascular actions of CGRP in the rat commented that changes in HR could occur in the absence of falls in MBP (Fisher *et al.*, 1983) a more recent investigation (Lappe *et al.*, 1987) showed that falls in calculated total peripheral resistance and increases in cardiac output occurred with doses of CGRP that did not increase HR significantly. However, higher doses of CGRP, with substantial hypotensive effects, caused tachycardia that was reduced, but not abolished, by propranolol (Lappe *et al.*, 1987). On balance, then, it seems likely that the direct chronotropic effects of CGRP will be difficult to separate from its hypotensive and reflex cardiac effects *in vivo*, but it is an intriguing possibility that the inotropic and afterload-reducing actions of CGRP infusions may be exerted with little influence on MBP or HR *in vivo* (Lappe *et al.*, 1987). Such a profile of action might be particularly useful in the treatment of problems such as congestive heart failure. It remains to be determined whether or not human α - or β -CGRP is more effective in this regard.

We were unable to show that infusion of human α - or β -CGRP at a low dose ($0.006 \text{ nmol h}^{-1}$) caused mesenteric vasodilatation. On the contrary, human α -CGRP at this dose, caused a slight but significant reduction in mesenteric flow. It may be that the mesenteric vascular bed is a primary target for baroreflex-mediated changes in sympathetic efferent outflow and such effects obscure any local vasodilator effects of CGRP on the mesenteric vasculature (Marshall *et al.*, 1986a; Kawasaki *et al.*, 1988). This conclusion is consistent with the finding that mesen-

teric vasodilatation can be elicited by bolus administration of rat α -CGRP (Gardiner *et al.*, 1988) where the rapidity of onset of vasodilator effect may outstrip 'on-line' baroreflex compensation.

The present study has shown that human α - and β -CGRP may differ in some of their regional haemodynamic effects, and that these differences may be dose-dependent. As mentioned above, the low dose of human α -CGRP appeared to cause a significant reduction in mesenteric blood flow, an effect not seen with human β -CGRP. Furthermore, the low dose of the latter appeared to cause a selective reduction in common carotid flow (associated with vasoconstriction) that did not occur with administration of human α -CGRP. This pattern of effects, in circumstances in which the actions of human α - and β -CGRP were compared in the same animals, makes it unlikely that the differences were attributable to a lack of comparability in the effective doses of the two peptides administered to the animals, due to differences in peptide activity, or to metabolism (Brown & Morice, 1987), for example. This assertion is supported by the finding that the pattern of change in HR and mesenteric flow were similar with both peptides given at 0.06 nmol h^{-1} , but at this dose the change in MBP was less significant for human β - than for human α -CGRP, consistent with the lesser hindquarters and carotid vasodilator effects of the former peptide.

Our finding of more marked vasodilator and hypotensive effects of human α - than of human β -CGRP is in agreement with some observations made *in vivo* (Franco-Cereceda *et al.*, 1987; Brown & Morice, 1987), but not with others (Brain *et al.*, 1986; Williams *et al.*, 1988). Differential metabolism, (due to the presence of a methionine residue in β -CGRP), could explain a lesser bioactivity of human β - than of α -CGRP given intravenously, and the finding that β -CGRP may be more potent than α -CGRP *in vitro* (Holman *et al.*, 1986), although recent studies have not found this (Mulder *et al.*, 1988). However, it is difficult to reconcile the differences between the results of studies in which human α - and β -CGRP were given locally (Brown & Morice, 1987; Williams *et al.*, 1988), unless the actual amounts of biologically active α - and β -CGRP delivered to the tissues were different.

Infusions of human α - and β -CGRP at 0.6 nmol h^{-1} produced similar regional haemodynamic effects; although the increases in HR were

the same, the fall in MBP tended to be less with human β - than with human α -CGRP. As mentioned above, it is possible these two peptides have different effects on cardiac output and this should be investigated formally.

Comparison of the present results with our previous findings (Gardiner *et al.*, 1989) highlights some differences in the haemodynamic effects of rat and human α -CGRP. With infusion of rat α -CGRP at 0.06 nmol h^{-1} there were renal, mesenteric, hindquarters and common carotid vasodilatations, although only in the latter vascular bed was there an increase in blood flow (Gardiner *et al.*, 1989). In the present study, infusion of human α -CGRP at the same rate caused changes in carotid haemodynamics similar to those seen with rat α -CGRP, but unlike the latter, human α -CGRP also caused an increase in hindquarters and a slight decrease in mesenteric flow. These differences are consistent with the slightly greater hypotensive and tachycardiac effects of human, compared to rat, α -CGRP (Gardiner *et al.*, 1989). However, the similarity in the changes in carotid haemodynamics with the two peptides argues against differences in amounts of active peptide administered explaining the difference in profiles of effect. This proposition is supported by the findings that with a higher infusion rate (0.6 nmol h^{-1}) the changes in hindquarters haemodynamics were similar with rat and human α -CGRP, but the carotid hyperaemia and the mesenteric vasoconstriction were greater with human than with rat α -CGRP (Gardiner *et al.*, 1989). A greater overall dilator effect of human compared to rat α -CGRP would be in line with the finding that the tachycardiac and hypotensive actions of the former were more marked than the latter at a dose of 0.6 nmol h^{-1} (Gardiner *et al.*, 1989). However, *in vitro* studies indicate that rat α -CGRP has more potent cardiac effects than human α -CGRP (Marshall *et al.*, 1986b; Holman *et al.*, 1986).

In summary, from the present, and previous results it appears that, *in vivo*, human α -CGRP may be a more potent carotid and hindquarters vasodilator than either human β - or rat α -CGRP. It is feasible these peptides also have differential effects on cardiac haemodynamics, but specific experiments are needed to address this possibility.

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